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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,679	03/11/2005	Thomas Felzmann	4518-0110PUS1	7223

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
04/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,679	FELZMANN, THOMAS	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-9,12,13,15,16,18,19 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *12,13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,18,19 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Declaration under 37 C.F.R. 1.132 of Dr. Thomas Felzmann submitted on 13 February 2009 is acknowledged. Applicant's amendment of the claims received on 13 February 2009 has been entered. Applicant's remarks submitted on 13 February 2009 are acknowledged.

Claims 10, 11, 14, 17 and 20 are cancelled. Claims 22-26 have been added. Claims 1-9, 12, 13, 15, 16, 18, 19 and 21-26 are pending. Claims 12, 13, 15 and 16 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1-9, 18, 19 and 21-26 are under examination.

Claim Objections/Rejections Withdrawn

The rejection of claims 17 and 20 under 35 U.S.C. 102(b) as being anticipated by Fong et al. (Annu. Rev. Immunol., 2000, 18:245-273), is withdrawn in response to Applicant's cancellation of the claims.

The rejection of claims 1, 3-5, 9, 18, 19 and 21 under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al. (Eur. J. Immunol., 2000, 30:3291-3298), is withdrawn in response to Applicant's amendment of the claims to limit the exposure time of dendritic cells to LPS and IFNγ.

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al., and further in view of Asavaroengchai et al. (PNAS,

2002, Jan. 22, Vol. 99:931-936), is withdrawn in response to Applicant's amendment of the claims to limit the exposure time of dendritic cells to LPS and IFNγ.

The rejection of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al., and further in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159) and Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250) ("Felzmann (2000)"), is withdrawn in response to Applicant's amendment of the claims to limit the exposure time of dendritic cells to LPS and IFNγ.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 9, 18, 19 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1, which has a priority filing data on 6 September 2002).

The instant claims are directed to a method for the treatment of a tumor which comprises, or consists essentially of (claim 21), administering to a patient in need thereof an effective amount of active dendritic cells (DC) that are tumor-specific and secrete IL-12, said DC being prepared by a process comprising, or consisting essentially of (claims 19 and 21): (a) collecting DC or DC precursor cells from a suitable

source to obtain a DC culture; (b) loading the DC of said DC culture with a tumor specific antigen, e.g., an antigen from a tumor cell from the patient having said tumor; and (c) exposing said DC culture to a concentration of LPS and a concentration of IFN-γ, effective to trigger the DC of said DC culture to secrete IL-12, wherein said exposure to LPS and IFN-γ occurs over a period of 1-10 hours, e.g., 2 hours, 6 hours, 2-10 hours, or 2-6 hours (claims 1, 5, 18, 19, 21 and 23-26); wherein the tumor is an advanced malignancy (claim 3); wherein said DC are collected from the patient having said tumor or from a bone marrow donor (claim 4); and wherein the DC have been generated *in vitro* from peripheral blood mononuclear cells (PBMCs) (claim 9); wherein said active DCs are administered or frozen after exposure to LPS and IFNγ (claim 22).

Bosch teaches a method for inducing maturation of immature dendritic cells (DCs) and priming those cells for an antigen-specific cytotoxic T cell response [0010]. Bosch teaches that DCs are increasingly prepared *ex vivo* for use in immunotherapy, particularly, immunotherapy of cancer [0002]. Bosch teaches that the method for producing a mature DC population *ex vivo*, comprises: (a) providing immature DCs, such as isolating autologous or allogenic DC precursors and immature DCs from blood (e.g., leukocyte population) and bone marrow [0021] [0029]; and (b) contacting the immature DCs with an effective concentration of BCG and IFN-γ under culture conditions suitable for maturation of the immature DCs [0010]. Bosch teaches that the mature DC population produces IL-12 [0010]. Bosch teaches that the immature DCs can be contacted with a predetermined antigen, such as a tumor specific antigen, or a tumor associated antigen (e.g., whole cells, tumor cell lysate, isolated antigens from

tumors [0044]), prior to or during contacting with BCG and IFNγ [0010]. Bosch teaches that the immature DCs are typically contacted with effective amount of BCG and IFNγ for about 1-24 hours [0040]. Bosch teaches that the mature DCs can be administered to an animal (human or non-human animal) [0019] [0021]. Bosch further teaches that combining IFNγ with certain DC maturation factors, such as bacterial lipopolysaccharide (LPS) and CD40 (each of the factors has a known capacity to induce a small amount of IL-12), can also enhance IL-12 production by dendritic cells [0006].

Although Bosch does not teach the time range to expose the immature DCs to a combination of LPS and IFNγ, it would have been *prima facie* obvious to one of the ordinary skill in the art at the time the invention was made to apply this parameter, i.e., 1-24 hour exposure time, to the DC maturation protocol. One of ordinary skill in the art would have been motivated to do so because Bosch teaches contacting the immature DCs with a combination of BCG and IFNγ for about 1-24 hours a to induce DC maturation *ex vivo* and priming those cells for an antigen-specific cytotoxic T cell response, thereby using these cells for cancer immunotherapy, and Bosch also teaches that other DC maturation factors, including LPS, can also be combined with IFNγ to enhance IL-12 production and potentiate dendritic cells. Further, using the exposure time for the DC maturation protocol with LPS and IFNγ amounts to a simple substitution of one known, equivalent element for another to obtain predictable results. This leads to the reasonably expected success due to ordinary skill and common sense, not innovation. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20,

(Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Also, although Bosch does not teach the same range of exposure time as recited in the claims, i.e., a period of 1-10 hours, Bosch, however, teaches the exposure time for about 1-24 hours, which overlaps the claimed time range. Given that the level of skill in this art is very high, and that optimizing parameters such as exposure time is routine, modifying the exposure time of Bosch to 1-10 hours would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success, absent evidence of unexpected results. As was found in In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), where the general conditions of a claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Applicant argues that because LPS is a toxin which causes septic or enterotoxin shock in humans, LPS would not have been used by one of skill in the art at the time of filing due to its toxic effects. Applicant's argument has been fully considered but has not been found to be persuasive. As set forth in the previous office action, in the cancer immunotherapy strategy of using *ex vivo* activated, tumor antigen-pulsed DCs, only the dendritic cells, but not free protein (e.g., LPS which is used to induce DC maturation), are administered to patients. After the incubation (pulsing and activating steps), the DCs were extensively washed to remove free protein, resuspended in sterile saline, and

administered to the patients by intravenous infusion (see Fong et al. pp. 259, top paragraph, reference provided previously).

Applicant argues that the specification has demonstrated unexpected results, for example, Fig. 9 shows that exposure of the DCs to IFN-γ and LPS for a period of 2-hour shows active DCs which have a therapeutic effect compared to a 24-hour exposure which shows exhausted DCs; and the clinical data indicates that several of the patients had stable disease for a prolonged period of time (pp. 22, lines 19-20). Applicant argues that the specification distinguishes "active DCs" which produce IL-12 from "exhausted DCs" which "do not produce IL-12 any more" (pp. 4, lines 5-6), and in order to capitalize on the IL-12, the specification states that: “it is, however, important to deliver the DCs according to the present invention in a state, where IL-12 release still takes place, i.e. immediately after the preparation of the tumor- or pathogen-specific IL-12 releasing DCs, or at least within 10, especially within 2-6 hours thereafter, ideally about 2 hours after completion of the preparation.” Applicant further provides Declaration under 37 C.F.R. § 1.132 by Dr. Thomas Felzmann, which refers to a post-filing publication by the inventor (cancer Immunol. Immunother., 2005, Vol. 54:769-780, “Felzmann et al. publication”) as evidence that these unexpected results are not limited to the 2-hour exposure time. Applicant argues that in the Felzmann et al. publication, cells incubated for 6 hours with LPS and IFNγ had “sustained release” of IL-12, whereas DCs exposed for 48 h no longer secreted IL-12. Applicant argues that it is reasonable to expect that the 10-hour time point would show the same results as the 6-hour time point.

Applicant's arguments and the Declaration of Dr. Thomas Felzmann under 37 C.F.R. § 1.132 filed 13 February 2009 have been considered, but are not sufficient to overcome the rejection under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), for reasons as set forth above for the following reasons.

The exposure time taught by Bosch (i.e., 1-24 hours) substantially overlaps that of the instantly claimed exposure time (i.e., 1-10 hours), in other words, Bosch expressly teaches short exposure, e.g., 1-, 2-, 3-hour. Given that the level of skill in this art is very high, and that optimizing exposure time, especially within a narrow time window (1-24 hours), is routine, modifying the exposure time of Bosch to 1-10 hours would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention, with a reasonable expectation of success, absent evidence of unexpected results. As was found in In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), where the general conditions of a claims are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Further, even Applicant has provided unexpected results for a short exposure of 2-6 hours, shown in the Felzmann et al. publication referred by the Felzmann Declaration (02/13/2009), Applicant has not demonstrated that a broader range, i.e., 1-10 hours, would result in similar effects. One cannot assume that "the 10-hour time point would show the same results as the 6-hour time point", given that a 24-hour exposure diminishes the therapeutic effect. This is because in the Felzmann et al. publication, "semi-mature" actively IL-12-secreting type 1 DC (sm-DC1) only refers to DCs stimulated with LPS and IFNγ for a short exposure of 2-6 hours (pp. 772, col. 1, 1st

paragraph in "Results"). The Felzmann et al. publication describes that "within the first 24 h after exposure to LPS and IFN-γ, DC trigger strong Th1 responses (i.e., IL-12 secretion), whereas at later time points, the same DC preferentially prime Th2 responses (pp. 770, col. 1, top bridging paragraph). Therefore, even DCs exposed to LPS and IFN-γ within the first 24 h still secret IL-12, these cells are not all qualified as "sm-DC1", with the exception of those exposed for 2-6 hours. Therefore, without supporting evidence, one cannot assert that the 10-hour time point would show the same results as the 6-hour time point, and cannot assume the same unexpected results for a broader time frame.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Asavaroengchai et al. (PNAS, 2002, Jan. 22, Vol. 99:931-936, reference provided previously).

Bosch teaches as set forth above. Bosch, however, does not teach that the treatment is performed after bone marrow transplantation (claim 2).

Asavaroengchai et al. teach that bone marrow transplants (BMT) or peripheral stem cell transplants are currently being used for the treatment of hematopoietic and solid tumors, and combining suitable immunization approaches with BMT can overcome tumor induced defects in the host anti-tumor immune response. Asavaroengchai et al. teach that in a therapeutic setting tumor antigen-pulsed DCs can have an impact on residual tumor that remains following BMT (pp. 931, see Abstract and Introduction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bosch with those of Asavaroengchai et al. to perform the treatment after bone marrow transplantation. One of ordinary skill in the art would have been motivated to combine the teachings, because Bosch teaches a method of immunotherapy using tumor antigen pulsed DC that release IL-12 upon maturation with LPS and IFN-γ, Asavaroengchai et al. teach that tumor-pulsed DC can have impact on residual tumor that remains following BMT. Therefore, the teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch (US 2005/0059151 A1), in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159), and Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250, "Felzmann (2000)"), both references provided previously).

Bosch teaches as set forth above. Bosch, however, does not teach that the DCs are additionally charged with a tracer antigen (claim 6) that is keyhole limpet hemocyanine (KLH) (claim 7), or additionally charged with an adjuvant tetanus toxoid (claim 8).

Rieser teaches using KLH as a tracer molecule for the determination of the magnitude, kinetics, and T-helper type-1 bias of the cellular and humoral immune response induced by DC-based immunization (pp. 151, see Abstract).

Felzmann (2000) teaches Xenogenization by tetanus toxoid (TT) loading into human tumor cells for anti-tumor immune therapy (pp. 241, Abstract). Felzmann (2000) teaches that unresponsiveness to tumor associated antigens (TAAs) could be overcome when a mixture of TAAs was used together with class II restricted peptides from TT for cell pulsing in vitro (pp. 241, Introduction, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Bosch, with those of Rieser and Felzmann (2000), to additionally load DC with a tracer antigen KLH and an adjuvant tetanus toxoid. One of ordinary skill in the art would have been motivated to combine the teachings, because Bosch teaches a method of immune therapy using tumor antigen pulsed DC that release IL-12 upon maturation with LPS and IFN-γ, Rieser teaches using KLH as a tracer molecule for determination of the kinetics of the immune therapy, and Felzmann (2000) teaches tetanus toxoid (TT) loading into human tumor cells enhances responsiveness to tumor associated antigens. Therefore, the teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 recites the limitation "said active DC" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Objections

Claim 18 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
April 16, 2009

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646